

## **Renal syndromes leading to abnormal kidney function:**

An abnormality in kidney function can be detected by the following:

- 1) changes in serum creatinine concentration, reflecting changes in GFR
- 2) abnormalities in urinalysis
- 3) altered renal homeostatic mechanisms: for example, abnormal volume regulation, hypertension, abnormal electrolyte profiles, metabolic acidosis, abnormal calcium phosphorus metabolism, anemia.
- 4) abnormal renal imaging studies

Although there are numerous disease states and conditions which can lead to altered kidney function, there are relatively few renal syndromes. Any condition affecting the function of the kidney should address the following questions:

- 1) does this represent an acute or chronic process?
- 2) is the process primarily glomerular, tubular, or vascular in origin?
- 3) is the process inflammatory or noninflammatory?
- 4) is the process associated with an underlying systemic disease?
- 5) is this prerenal, intrinsic renal, or postrenal in origin?

The following is a list of syndromes associated with intrinsic renal disease. Disease processes that alter kidney function must cause abnormalities in one of the following structures: glomeruli, tubules or interstitial areas (tubulointerstitial areas), or renal vasculature.

Glomerular syndromes:

nephrotic syndrome

nephritic syndrome

rapidly progressive glomerulonephritis (the most severe form of the nephritic syndrome)

mixed nephritic nephrotic syndrome

mesangial pattern

chronic glomerular disease

Tubular syndromes:

noninflammatory tubular interstitial changes

inflammatory tubular interstitial changes

acute pyelonephritis

allergic interstitial nephritis (a form of inflammatory tubular interstitial disease)

chronic interstitial disease

Vascular syndromes:

prerenal azotemia (reduced renal blood flow or reduced renal perfusion pressure)

renal artery stenosis (unilateral or bilateral)

hypertensive nephrosclerosis (ischemic nephropathy)

vasculitis (typically presents as nephritic syndrome)

## Typical Features of the Main Renal Syndromes

### Glomerular Syndromes:

**I) Nephrotic syndrome:** the pathognomonic abnormality is abnormal permeability of the glomerular capillary wall to protein, leading to proteinuria. Since the major serum protein is albumin the majority of urinary protein excretion in nephrotic syndrome will be albumin. Clinical definition: proteinuria, hypoalbuminemia, edema formation, lipiduria. To produce this syndrome, urinary protein excretion is typically > 3 g per day, corresponding to a spot urine protein creatinine ratio of > 3, and urinary dipstick 3+ to 4+ positive for protein. This level of proteinuria can be thought of as nephrotic range proteinuria. Patients with this level of proteinuria have glomerular disease. Many patients, however, may have this degree of proteinuria without the development of the complete clinical syndrome: i.e., they may have minimal or no edema and relatively normal serum albumin concentration.

Patients with pure nephrotic syndrome typically have normal glomerular filtration rate, normal blood pressure, normal acid-base status. The edema is a consequence of avid sodium retention by the kidney as a result of enhanced renal tubular sodium reabsorption (particularly in the distal tubule). The retained salt and water is primarily restricted to extracellular fluid volume. Because of decreased plasma oncotic pressure (due to albuminuria), there is disproportionate increase in the size of the interstitial fluid volume. The plasma volume remains normal, until there is profound hypoalbuminemia (<2g/dl). There may be associated pleural effusions and ascites with severe volume retention. Since intravascular volume remains normal, pulmonary edema is not a feature of nephrotic syndrome. Hypercholesterolemia is frequently present with nephrotic syndrome.

Typical urinary findings: 3+ to 4+ positive dipstick for protein (dipstick is specific for albumin). Remainder of the dipstick tests are normal. Urinary concentration is intact. Urinary sediment: generally unremarkable. There may be oval fat bodies and fatty casts related to lipiduria. Clinical examples: most common cause in children is minimal change disease. Most common intrinsic glomerular disease leading to nephrotic syndrome in Caucasian adults is membranous glomerulopathy. Most common cause in African-American adults is focal segmental glomerulosclerosis and second leading cause in this population is membranous glomerulopathy.

Some of the diseases leading to nephrotic syndrome can progress to chronic renal insufficiency. This is particularly true for focal segmental glomerulosclerosis, but may also occur with membranous glomerulopathy. Chronic renal disease is extremely unusual with minimal change disease.

The most common cause of nephrotic syndrome in adults is diabetic nephropathy. Diabetic nephropathy is a slowly developing noninflammatory process which is first clinically detected by the presence of microalbuminuria and later with overt proteinuria, frequently leading to nephrotic syndrome. By the time heavy proteinuria is present there is also decreasing glomerular filtration rate. The disease progresses to chronic renal insufficiency and ultimately end-stage renal disease. Diabetic nephropathy is the most common etiology for end-stage renal disease in the United States.

Disease states which lead to nephrotic syndrome and chronic renal insufficiency are frequently

associated with hypertension and other alterations in homeostasis related to chronic renal insufficiency (decreased GFR).

The diseases mentioned in this section described noninflammatory glomerular diseases which lead to abnormal permeability of the glomerular capillary wall to protein. Disease states which lead to inflammatory glomerular changes are discussed in the subsequent sections.

**II) Nephritic syndrome:** the pathognomonic feature of nephritic syndrome is the presence of inflammatory changes within the glomerulus. Inflammatory changes are often accompanied by pro inflammatory cytokines and mediators, complement activation, proliferation of mesangial cells, infiltration of glomerulus by inflammatory cells (mononuclear and PMN's), endothelial cell swelling. Net result of these histologic changes is decreased surface area for glomerular filtration, leading to decreased GFR.

Inflammation predictably leads to glomerular hematuria. Red cells excreted into the urine are often crenated and dysmorphic in appearance. Red blood cells may become incorporated into the Tamm Horsfall protein matrix producing red blood cell casts. Red blood cell casts are pathognomonic for intense glomerular inflammation. Hematuria can be either micro or macro hematuria. The absence of any type of hematuria strongly argues against the presence of glomerular inflammation.

There may also be abnormal permeability of the glomerular capillary wall to protein. However, the decreased GFR leads to less quantitative proteinuria. The level of protein excretion is generally less than 2 g per day, corresponding to urine protein creatinine ratio of approximately < 2, and urinary dipstick approximately 2+ or less for protein. Since there is less albuminuria, serum albumin concentration and plasma oncotic pressure remain near normal. The decreased GFR and changes in Starling's forces in peritubular capillaries lead to avid salt and water retention. Given the normal plasma oncotic pressure, this means there is considerable increase in plasma volume and interstitial fluid volume. Increased blood volume will be manifest as hypertension pulmonary congestion, in addition to interstitial edema. Thus, these patients can present with pulmonary edema.

Clinical examples: poststreptococcal glomerulonephritis is the prototype. All forms of rapidly progressive glomerulonephritis (RPGN) represent examples of the nephritic syndrome, which by definition are severe enough to cause rapidly progressive renal failure.

Some, but not all, forms of nephritic syndrome may have evidence for complement activation and may also have specific serologic markers for systemic diseases.

### **III) Mixed nephritic nephrotic syndrome:**

These patients have features of both nephritic and nephrotic syndromes. There will be evidence for inflammatory glomerular disease, such as hematuria, red blood cell casts, and worsening GFR. In addition there is nephrotic range proteinuria often leading to hypoalbuminemia.

Clinical examples: SLE, diffuse proliferative form is the prototype. Other examples include membranoproliferative glomerulonephritis (idiopathic forms and secondary forms, such as hepatitis C related)

### **IV) Mesangial pattern:**

Some forms of glomerulonephritis lead to inflammatory changes which are restricted to the mesangial area of the glomerulus. This leaves the remainder of the glomerular capillary loop

unaffected. Since the glomerular capillary wall is relatively well preserved, GFR is typically normal and there is minimal proteinuria. However, the presence of mesangial inflammation does lead to hematuria, which can be either microscopic or macroscopic. Red blood cell casts may be present. Since GFR is preserved and there is minimal proteinuria, there is typically no evidence for volume expansion, hypertension, or edema formation.

Clinical examples: IGA nephropathy is the prototype. The IGA immune deposits are restricted to the mesangium. SLE may also be associated with immune deposits restricted to the mesangium.

#### **V) Chronic glomerulonephritis:**

Chronic glomerular disease is typically recognized by the presence of abnormal urinalysis and abnormal GFR (increased serum creatinine concentration, ie, chronic renal insufficiency). Chronic renal insufficiency is due to a decreased number of functioning nephrons, and tends to be inexorably progressive. This syndrome is typically recognized by review of serial laboratory tests (UA and creatinine). Common urinary findings include chronic proteinuria of varying degrees, chronic microhematuria, or both proteinuria and hematuria. Chronic renal insufficiency frequently leads to decreased size kidneys, typically described as bilaterally symmetrical decreased size with increased echogenicity by ultrasound imaging.

Urinary findings unique to this setting: waxy casts, seen in any form of chronic renal insufficiency. They are not helpful in determining etiology of the renal disease. Waxy casts simply denote the presence of chronicity.

#### **Tubular syndromes:**

##### **I) Noninflammatory tubulointerstitial disease:**

In this setting, tubules and renal interstitium have been damaged by noninflammatory mechanisms. Damaged tubules have impaired ability to reabsorb glomerular filtrate, leading to the increased intratubular pressures. This dissipates the hydrostatic pressure gradient between the glomerular capillary and the renal tubule and therefore decreases glomerular filtration. In short, when the renal tubule fails to reabsorb, glomerular filtration decreases, even though the glomerulus is histologically intact.

Clinical findings: acute decrease in GFR, increased serum creatinine. urinalysis findings: there will be minimal proteinuria, since glomeruli are normal. There is frequently minimal or absent hematuria. Urinary specific gravity is typically 1.010, corresponding to urine osmolality of ~ 300mosm/kd, which is similar to plasma osmolality. This is known as isosthenuric urine. The damaged renal tubule can neither concentrate nor dilute the urine, thus, urine osmolality is the same as the initial glomerular filtrate which is always has the same osmolality as plasma. The remainder of the urinary dipstick is typically unremarkable. Urinary sediment abnormalities: granular casts are the hallmark feature. The granular material represents fragments of cellular debris from injured cells. There may also be sloughed renal tubular epithelial cells. These may become incorporated into casts, renal tubular cell casts. There are no inflammatory cells. Clinical examples: acute tubular necrosis is the prototype. Renal tubules are damaged by prolonged ischemia. Oxygen consumption by the kidney is done by the renal tubules, thus they are most susceptible to ischemic injury. Direct renal tubular nephrotoxic agents are also common causes of noninflammatory tubular injury. Examples include aminoglycosides, amphotericin B., heavy metals, cisplatin, intravenous contrast media, cyclosporine, tacrolimus, lithium, myoglobin,

free hemoglobin. In each of the examples the agent is directly nephrotoxic to renal tubular cells.

A direct inflammatory response is not a typical feature and is not necessary to produce tubular injury. The absence of inflammatory response is suggested by the relative absence of inflammatory cells (wbc) and red blood cells in the urinary sediment.

## **II) Inflammatory tubular interstitial injury:**

In this setting, renal tubules are being directly injured by an active inflammatory response. The inflammatory cells are frequently mononuclear cells, but may also include eosinophils and neutrophils.

Urinary findings: the findings in the urinary specific gravity, urine osmolality, and urinary dipstick are similar to those in noninflammatory tubular diseases. Additional findings, however, may include positive leukocyte esterase, when urinary neutrophils are present, and microscopic hematuria.

Clinical examples: acute kidney transplant rejection would be the prototype example. In this case the allograft is recognized as foreign antigen and an immune response is directed against the renal tubular cells which express histocompatibility antigens.

Other examples include allergic interstitial nephritis, which is typically precipitated by medications or viral infections in an idiosyncratic manner. The viral or drug antigens act as haptens, leading to an inflammatory immune response directed against renal tubules. Since this is an allergic response, some of the infiltrating cells are eosinophils, frequently leading to the presence of eosinophils in the urine. Urinary eosinophils are detected by Hansel's stain or by Wright's stain. Most of the urinary white blood cells are neutrophils. This represents sterile pyuria.

Drugs associated with allergic interstitial nephritis: Dilantin, allopurinol, beta-lactam antibiotics, sulfa derivatives antibiotics, cimetidine.

## **III) Acute pyelonephritis: (acute bacterial infection leading to inflammatory tubular injury):**

ascending bacterial infection leading to bacterial infection and neutrophil inflammatory response in the medulla. Typically unilateral, leading to decreased function of the affected kidney.

Untreated, it can lead to urosepsis and destruction of renal parenchyma.

Urinary findings: leukocyte esterase positive, frequently nitrite positive, frequently positive for blood (blood is from the urinary tract rather than kidney). Urinary sediment has marked pyuria, white blood cell clumps, and bacteria. There may be white blood cell casts. Urine cultures will be positive.

**IV) Chronic pyelonephritis:** generally results as a complication of urinary tract infections in the presence of structural abnormalities of the urinary tract, particularly those which lead to urinary tract obstruction. Leads to changes including focal scars within the kidney with loss of functioning renal parenchyma.

**V) Obstructive uropathy:** obstruction to urinary flow leads to increased pressures which are transmitted back to the renal tubule and therefore lead to decreased glomerular filtration rate. Obstructed tubules cannot perform normal tubular function such that isosthenuric urine will be formed and fractional excretion of sodium will be  $> 1\%$  Patients frequently report symptoms related to bladder outlet obstruction.

Urinary findings: minimal proteinuria. Variable degree of hematuria (red blood cells will be coming from the urinary tract rather than kidney). In the absence of infection there will be no evidence of inflammation, ie, minimal pyuria. Renal imaging studies are essential in evaluating

obstruction. If the obstruction is not relieved, permanent renal injury can occur.

#### **VI) Chronic interstitial renal disease:**

This will be manifested as chronic renal insufficiency, increased serum creatinine concentration. The other typical signs and symptoms of chronic renal insufficiency may be present, such as anemia and abnormal calcium phosphorus metabolism. Urinary findings: minimal proteinuria, typically < 1 gram daily. In the absence of any active inflammation there will be minimal hematuria and no pyuria or bacteria. Renal imaging studies typically show decreased sized kidneys with increased echogenicity.

Clinical examples: analgesic nephropathy, chronic pyelonephritis, chronic obstructive uropathy, chronic cyclosporine toxicity, chronic lithium toxicity.

#### **Vascular syndromes:**

**I) Prerenal azotemia:** in this setting, the renal parenchyma is normal and the urinary drainage system is normal. The abnormality consists of either decreased renal blood flow or decreased renal perfusion pressure or a combination of these two factors. Each kidney normally receives ten percent of total cardiac output in order to produce a normal glomerular filtration rate. In the presence of decreased renal blood flow or perfusion pressure, renal autoregulation occurs such that GFR is well maintained despite moderate changes in renal blood flow or arterial pressure. In severely decreased flow or perfusion, however the renal autoregulatory response is overwhelmed and GFR becomes decreased. Medications which interfere with renal autoregulation will precipitate acute renal failure with less severely decreased renal blood flow and perfusion pressure. (For example, ACE inhibitors, angiotensin II receptor blockers, NSAIDs) common precipitating events: any cause of hypovolemia. Any cause of severe hypotension. Decreased cardiac output from cardiac etiology (decreased systolic function, valvular disease, pericardial tamponade, arrhythmias) urinary findings: the urinalysis is normal, as the kidney is inherently normal. Urinary specific gravity is increased and urine osmolality is increased. Urinary dipstick is normal. Urinary sediment is normal. Hyaline casts are frequently seen in the concentrated urine.

Renal imaging studies are normal.

Treatment is directed to correcting the underlying cause of decreased renal blood flow or renal perfusion pressure.

Laboratory findings: there is an elevated BUN to creatinine ratio (typically > 20 to 1). Serum creatinine is a function of GFR. BUN is a function of GFR and urinary flow rate. Situations associated with decreased urinary flow rate lead to increased renal tubular urea reabsorption, leading to disproportionate increases in BUN, relative to creatinine. Prerenal factors are associated with decreased urinary flow rate.

**II )Renal artery stenosis:** unilateral renal artery stenosis leads to renin dependent hypertension but not to acute renal failure, since the opposite kidney has normal vasculature and function. ACE inhibitor or angiotensin II receptor blockers would be very effective in treating this form of hypertension and would not lead to acute renal failure. They would lead to decreased GFR in the stenotic kidney which is dependent on autoregulatory response to make GFR. Bilateral renal artery stenosis frequently leads to volume dependent hypertension and reduced GFR. Drugs which interfere with autoregulation in this setting will often precipitate acute renal failure. Urinary findings are usually normal in unilateral renal artery stenosis. In bilateral renal artery

stenosis, there is often mild to moderate proteinuria, but no evidence for an inflammatory response (no hematuria or pyuria)

**III) Hypertensive nephrosclerosis:** long-term uncontrolled hypertension leads to arteriolar nephrosclerosis in the microcirculation of the kidney. These progressive changes can lead to ischemic atrophy of glomeruli, and therefore decreased GFR. In this country, it is felt that this disease process is the second leading cause of end-stage renal disease, particularly in African-American populations. Urinary findings: nonnephrotic ranged proteinuria, typically < 1 gram daily. No evidence for inflammatory reaction (no hematuria or pyuria). Renal imaging studies show bilaterally symmetrically decreased sized kidneys with increased echogenicity.

Episodes of malignant hypertension can lead to acute fibrinoid necrosis of the renal microcirculation. In this setting there is frequently increased proteinuria, microhematuria, and rapid worsening of GFR. Untreated, it can rapidly lead to end-stage renal disease. There are also systemic features including microangiopathic hemolytic anemia, hypertensive encephalopathy.

**IV) Renal vasculitis:** diseases associated with vasculitis typically present as nephritic process. More severe involvement can lead to rapidly progressive glomerulonephritis. Clinical examples: ANCA associated RPGN, polyarteritis nodosa.

Hemolytic uremic syndromes: the primary pathologic defect is marked glomerular endothelial cell swelling and damage with platelet thrombi formation within the lumens of glomerular capillaries. This typically leads to acutely decreased GFR. Urinary findings will typically be nephritic. These syndromes are typically associated with thrombocytopenia and microangiopathic hemolytic anemia.